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Development of 11β-HSD1 inhibitors for the treatment of metabolic syndrome

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Summury. 11β-Hydroxysteroid dehydrogenase type I (11β-HSD1) is the enzyme that converts inactive 11-ketoglucocorticoids into active 11β-hydroxy-forms in metabolically relevant tissues such as the liver, adipose tissue and skeletal muscles. Chronically elevated local glucocorticoid action as a result of increased 11β-HSD1 activity is associated with metabolic syndrome, obesity, insulin resistance, type 2 diabetes mellitus and cardiovascular complications. Inhibition of 11β-HSD1 has been proposed as a strategy to suppress glucocorticoid action in tissue-specific manner. A large variety of 11β-HSD1 inhibitors from different series of nitrogen containing heterocycles are now under investigation to treat type 2 diabetes and obesity.

Keywords: 11β-hydroxysteroid dehydrogenase, cortisol, metabolic syndrome, obesity, drug development.

Introduction. Obesity and related diseases constitute a major health problem in modern society. It is associated with an increased risk of type 2 diabetes mellitus (T2DM), cardiovascular disease, stroke and certain types of cancer. The WHO has estimated that worldwide as many as 1.6 billion adults are overweight with at least 400 million of them clinically obese. Presumably by 2025, 40 % of men and 50 % of women will be obese [1, 2]. All of this has led to an increased recognition of the «metabolic syndrome» (MS) as a prediabetic state. The MS (syndrome X or insulin resistance syndrome) is characterized as a cluster of metabolic abnormalities that include central obesity, impaired glucose tolerance, elevated triglycerides, dyslipidemia, hypertension and subclinical chronic inflammation or prothrombotic states [3].

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Although over 80 % of all individuals with T2DM are either overweight or obese [4], not everyone suffering from obesity is equally at risk. As a matter of fact, the majority of obese individuals do not develop diabetes. Why is it so? The answer to this question is as follows. Different fat distributions are associated with different degrees of metabolic risk. Central/visceral obesity in particular is associated with impaired glucose tolerance and T2DM [5]. However, the molecular mechanisms underlying the obesity-related complications are complex and not fully understood. It has been noted that metabolic abnormalities found in diabetes and MS are similar to those observed in syndromes of prolonged glucocorticoid excess in blood (Cushing's syndrome) [3]. However, in patients with simple obesity or MS, the plasma glucocorticoid level is not notably elevated, whereas the metabolic clearance of these hormones or their metabolites is increased [6-8]. It has been hypothesized that local glucocorticoid

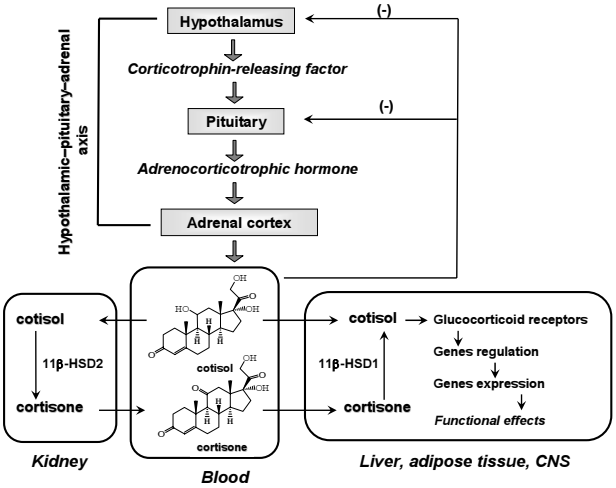


Fig. 1. Schematic representation of glucocorticoid metabolism and action.

generation is enhanced in white adipose tissue, and that the 11-β-hydroxysteroid dehydrogenase (11β-HSD) enzyme type 1 plays an essential role in this process. Recent studies have demonstrated that 11β-HSD1 is a novel molecular target for treating MS and T2DM, and that compounds inhibiting the activity of this enzyme provide promising opportunities for the development of therapeutic interventions [9-11].

The aim of our review is, first of all, to explain the importance of glucocorticoids in MS, to highlight some approaches that have been explored in an effort to find possible ways of reducing the action of these hormones in the liver and adipose tissue (as a basis for novel therapies of T2DM) and, finally, to survey structural types of 11β-HSD1 inhibitors.

The role of 11β-HSD1 in obesity and insulin resistance. Glucocorticoids (cortisol in humans or corticosterone in rodents) are hormones that play an important role in the body's response to stress as well as regulate energy metabolism and modulate inflammatory and immune responses. They promote gluconeogenesis in the liver and oppose the action of insulin by directly inhibiting β-cell insulin secretion in the pancreas and peripheral glucose uptake in the muscle. Glucocorticoids also increase lipolysis in adipose tissue, leading to fatty acid mobilization when the insulin action is low [12-16].

Cortisol is produced by the adrenal cortex and regulated by adrenocorticotrophic hormone (ACTH) under the control of the hypothalamic-pituitary-adrenal axis (HPA) (Fig. 1). ACTH production is induced by the corticotrophin-releasing factor (CRF), released from the hypothalamus, and by adrenalin in stress situations. By a negative feedback regulation, glucocorticoids inhibit their own production by decreasing the synthesis and release of CRF and of arginine vasopressin. About 96 % of the circulating 11-hydroxy glucocorticoids are protein-bound with 6 % to albumin and 90 % to corticosteroid binding globulin-α (CBG, transcortin). The «free hormone hypothesis» suggests that glucocorticoids bound to serum proteins are unable to enter a target cell and are therefore inactive; thus, the concentration of unbound «free» hormone at the target cell determines biological action [17]. The inactive 11-ketoglucocorticoids cortisone and 11-dehydrocorticosteron have low affinities to bind to CBG and albumin. They exist mostly in the free form and are able to enter target cells, where they undergo conversion to their active 11β-hydroxy forms. At a tissue-specific level, the glucocorticoid action is tightly controlled by 11β-HSD enzymes [18].

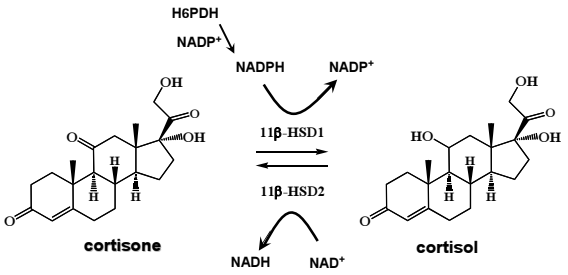


Fig. 2. Interconversion of cortisone and cortisol.

Almost 60 years ago D. Amelung and his coworkers discovered the enzymic interconversion of active 11-hydroxy glucocorticoids (cortisol, corticosterone) and inert 11-keto forms (cortisone, 11-dehydrocorticosterone) [9]. Two types of the 11β-HSD were identified. 11β-HSD1 is an NADPH-dependent enzyme, which converts inactive 11-keto forms of glucocorticoids to their active forms (cortisol, corticosterone) within the cells of key metabolic tissues including liver, adipose tissue, skeletal muscle and brain (Fig. 2). It belongs to the short-chain dehydrogenase/reductase family of enzymes, and contains 292 amino acid residues. However, the reductase activity predominates *in vivo* owing to the redox potential maintained by the NADPH-generating enzyme hexose-6-phosphate dehydroge-

nase (H6PDH) in the endoplasmic reticulum (ER) compartment [18-21].

Functionally, the enzyme 11β-HSD1 may be divided into four important regions. The transmembrane domain (residues 1-23 in humans), enabling the enzyme to attach itself to the lumen of the ER, the nucleotide binding domain (Rossmann fold), the catalytic site, and the C-terminal domain which plays an important role in the oligomerisation of the enzyme. Ser170-Tyr183-Lys187 — these three residues form the catalytic site, orient the substrate, and catalyze the proton transfer to and from the reaction intermediates [21-23].

An excessive 11β-HSD1-dependent local cortisol production increases hepatic glucose output and decreases glucose uptake in adipose tissue and skeletal muscles. Besides, it stimulates lipolysis, thereby leading to higher levels of free fatty acids, which contribute to the adverse metabolic effects of glucocorticoids. An elevated local cortisol level antagonizes the effects of insulin and leptin, thus contributing to the development of insulin resistance and T2DM [10, 11, 18]. In humans, the expression of 11β-HSD1 in adipose tissue is positively correlated with the degree of obesity and is acquired independently of genetic factors. This hypothesis was put forward in the investigation of young adult monozygotic twins, one of which was obese and the other lean. The 11β-HSD1 expression was elevated in obese twins as compared with their lean counterparts [24].

11β-HSD2 is a NAD^+-dependent dehydrogenase that catalyzes the reverse reaction of inactivating cortisol to cortisone. It contains 405 amino acid residues. Enzymes of this type are mainly localized in the mineralocorticoid receptor (MR) target tissues such as kidney, colon, salivary gland and the placenta where they function to protect the nonselective MR from excessive exposure to cortisol. The inhibiting activity of the 11β-HSD2 generates sodium retention, hypokalemia and hypertension [18, 25]. Thus, any 11β-HSD1 modulator would need to demonstrate selectivity over 11β-HSD2.

It has been hypothesized that decreasing the glucocorticoid activity in adipose tissue and liver might protect against obesity and MS [10, 11].

A potential role for 11β-HSD1 inhibitors in metabolic disease has been established with the help of rodent pharmacodynamic models for MS or diabetes, such as genetically obese Zucker rats and transgenic mice [26-29]. The results of these experiments are summarized in Table 1.

Table 1

The role of 11β-HSD1 in metabolic disease

11β-HSD1 over-expressing rodents	11β-HSD1 knockout mice
· Increased corticosterone production rate · Heavier weight and increased appetite · Visceral obesity · Hyperglycemia / Insulin resistant diabetes · Hypertentsion and hyperlipidemia	· Reduced weight gain · Improved insulin tolerance · Reduced visceral fat accumulation · «Diabetes-resistant» phenotype

On the one hand, rodents over-expressing 11β-HSD1 in adipose tissue or liver (aP2-HSD1 or apoE-HSD1 transgenic mice) exhibit several features of MS including abdominal obesity, glucose intolerance, dyslipidemia and others. On the other hand, the 11β-HSD1 knockout mice are resistant to diet-induced obesity and exhibit improved insulin sensitivity and lipid profiles. The administration of specific 11β-HSD1 inhibitors in animal models of insulin resistance led to improved hyperglycemia and insulin sensitivity [26, 28, 29].

Thus, selective inhibition of 11β-HSD1 has therefore been proposed as a novel drug target for treatment of disorders associated with cortisol excess such as obesity, insulin resistance and T2DM. Also, 11β-HSD1 inhibitors have been postulated to have a beneficial effect on cognitive impairment and other associated conditions [30, 31].

Development of 11β-HSD1 inhibitors. All known inhibitors of 11β-HSD1 could be divided into several groups: endogenous substances, exogenous natural products and their derivatives, and, finally, synthetic small organic molecules from different classes of heterocyclic compounds.

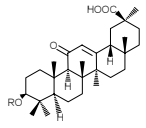
Several endogenous steroids, including progesterone, its metabolite (3α-5α-tetrahydro-11β-hydroxyprogesterone) and androgen metabolites such as 3α,5α-tetrahydro-11β-hydroxytestosterone, have proved to act as inhibitors of 11β-HSD enzymes, although none of the reported compounds is selective [32]. Furthermore, several bile acids, such as chenodeoxycholic

acid, inhibit 11β-HSDs, although their effect is not specific and rather weak [33].

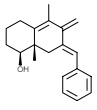
One of the first described and most widely known 11β-HSD inhibitors is glycyrrhizic acid, a compound derived from licorice, and its hydrolytic product glycyrrhetinic acid **1** (GA). Licorice is prepared from the plant *Glycyrrhizia glabra*. It has been used in medicine for over a thousand years. On the basis of 18β-glycyrrhetinic acid, the hemisuccinate carbenoxolon **2** (CBX) was synthesized for anti-ulcer treatment. As an anti-ulcer agent, it has been in use for almost 50 years [18, 34, 35]. CBX demonstrates liver-specific inhibition of 11β-HSD1, observed in both obese Zucker rats and humans with type 2 diabetes [35-40]. GA and CBX are potent inhibitors of 11β-HSD1, with IC_{50} in the nanomolar range. CBX gets bound to the active site of the enzyme by means of interacting with Leu 217, Ser 170 and Tyr 183 as well as with the co-factor [41].

Nevertheless, the pharmaceutical use of GA and CBX is limited by their unspecific action. Both compounds are also potent inhibitors of 11β-HSD2, which explains the undesired mineralocorticoid mediated side effects [42]. Besides, CBX has been reported to have a limited ability to penetrate adipose tissue, the target tissue where 11β-HSD1 inhibition is thought to be important for mitigating insulin resistance [43].

Other examples of natural 11β-HSD inhibitors are abietic acid **3**, a compound contained in wood products and used in cosmetics because of its anti-irritant and anti-inflammatory effects [44], as well as flavonoid naringenine **4** found in grapefruit juice [45], and anthraquinone emodin **5**, an active ingredient of *Rheum palmatum*. A recent investigation has proved the latter substance to be a potent and selective 11β-HSD1 inhibitor with the IC_{50} of 186 and 86 nM for human and mouse enzymes respectively [46].



1 R=H;
2 R=C(O)CH_2CH_2C(O)OH



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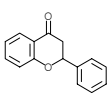

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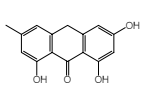

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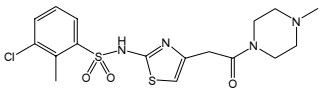
Interestingly enough, coffee has also been examined as a potential 11β-HSD1 inhibitor due to an antidiabetic effect that coffee consumption is supposed to have. Inhibition of 11β-HSD1 turned out to be seven- to tenfold higher than that of 11β-HSD2. Although coffee clearly demonstrates an inhibitory effect, it has not yet been established what kind of compounds contained in coffee are responsible for this action. It is also unknown whether the compounds in question are readily absorbed following oral ingestion [47].

Although the enzyme 11β-HSD1 was given a comprehensive scientific description back in the 1960s, it is only in 2001 that the first patent concerning its inhibitor was claimed. Today, 25 laboratories all over the world are investigating various classes of 11β-HSD1 inhibitors to find a potential treatment for metabolic diseases [40]. The modern approaches to the development of inhibitors makes use of the available target enzyme crystal structures for the purpose of structure-based design. The Protein Data Bank contains information on eighteen crystal structures of human 11β-HSD1 [48-52]. There are two structures of the mouse protein [52, 53] and three structures of the guinea pig protein [52, 54]. The availability of 11β-HSD1 crystal structures with their bound inhibitors helps to discover and design more potent and selective inhibitors. The crystal structures of rodent 11β-HSD1 are considerably different from those of the human enzyme; therefore designing a compound to inhibit the rodent enzyme will probably not produce the optimal inhibitor for the human enzyme. However, since numerous *in vivo* pharmacological studies are being carried out on rodents, it is useful for inhibitors of human 11β-HSD1 to also inhibit the rodent enzyme.

Several classes of 11β-HSD1 inhibitors are currently under investigation, many of them with nanomolar inhibition kinetics and reasonable metabolic profiles. The major chemical series of 11β-HSD1 inhibitors are shown below.

These compounds evolved from the hits identified by high-throughput screening of internal compound collections using an isolated human 11β-HSD1 enzyme. Then they have been studied in animal models of obesity, T2DM and atherosclerosis. Some patents list over 1000 examples of active compounds that display IC_{50} values of 0.4-1000 nM in enzyme assays and demonstrate improvement of metabolic parameters including reduced food intake, decreased



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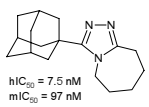

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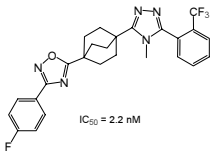

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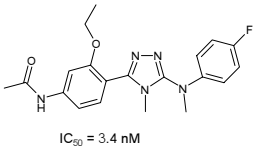

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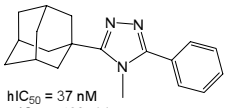

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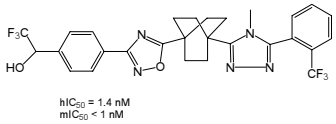

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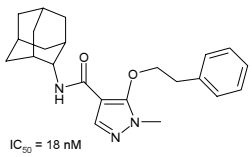

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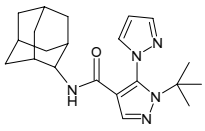

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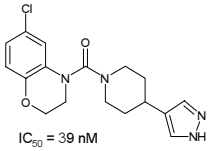

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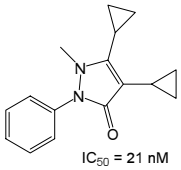

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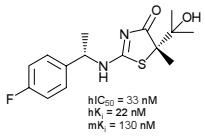

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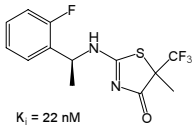

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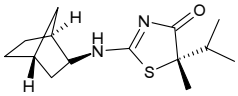

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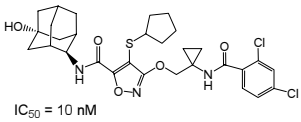

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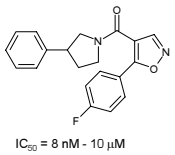

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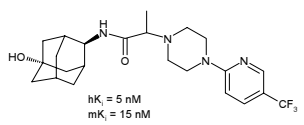
glucose levels, enhanced insulin sensitivity, improved lipid profiles and reduced atherosclerotic plaque progression in experiments *in vivo* [40, 55, 56]. Unfortunately, in many cases the structures or biological activities for specific compounds are not disclosed in the patents. The first and probably best-described 11β-HSD1 inhibitors belong to the class of arylsulfonamidothiazoles, e.g. compound **6**. *In vitro* they inhibit 11β-HSD1 at nanomolar concentrations, with a selectivity of at least 200-fold over 11β-HSD2 [57].

It has been discovered that adamantyl[1,2,4] triazolo[4,3-*a*]azepine **7**, the so-called compound 544, is a potent and selective inhibitor of 11β-HSD1, although it only displays a short-lived inhibition of murine 11β-HSD1 *in vivo* [58]. Modifications of the 1,2,4-triazole series led to several variable structural classes. All compounds **8-11** act against the human and mouse enzymes with compound **11** being the most potent in either case [59]. To put this in perspective, compound **8** displays an IC_{50} value of 2.2 nM, a good selectivity against 11β-HSD2 and a long-lived inhibition of murine 11β-HSD1 *in vivo* [60].

A series of 11β-HSD1 inhibitors containing pyrazole **12-14** or pyrazolone **15** core [61, 62], 2-aminothiazolone moiety **16-18** [63-65] and oxazole ring **19, 20** [66] have also been published. Compound **17** displays good potency against the recombinant enzyme (K_i=22 nM), in cellular assays (IC_{50}=33 nM) and has low clearance and high bioavailability in rats [64]. The 2-aminothiazolone **18** known as AMG-221 has entered Phase 1 clinical trials [35].

Cycloalkyl acetamides containing bulky lipophilic groups, such as adamantanyl ring systems, adjacent to the amide group (see, for instance, compounds **21-24**), have been patented and published by a number of different companies [67-73]. Compound **22**, has been proven to



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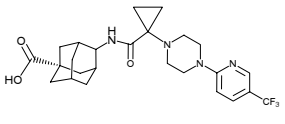

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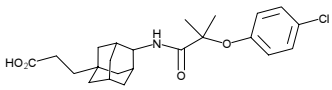

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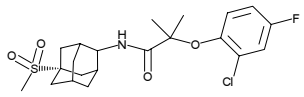

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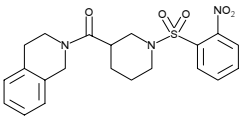

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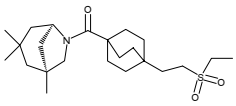

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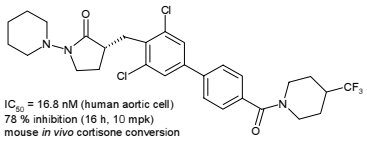

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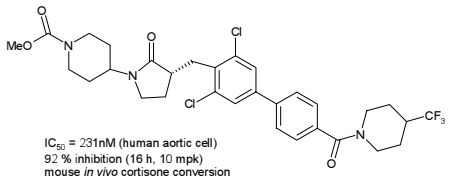

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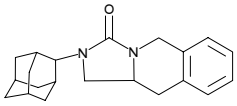

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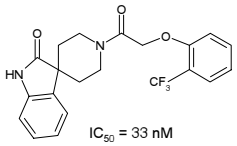

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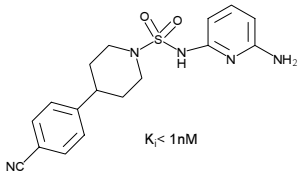

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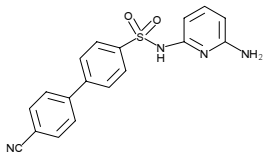

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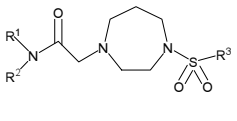

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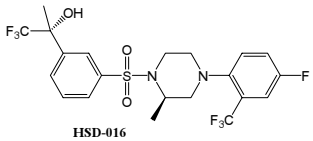

34

exert a potent and selective activity in enzyme and cellular assays [72]. Adamantanyl derivative **23** displayed high levels of inhibition of 11β-HSD1 in liver, and moderate levels in fat and brain after 16 hours of binding, with a good pharmacokinetic profile and moderate microsomal stability [73]. The similar 5-methylsulfonyl derivative **24** displayed potent tissue inhibition of 11β-HSD1 in liver, fat and brain, as well as high bioavailability, moderate clearance and a good volume of distribution in mice [74]. The crystal structures of these and similar compounds bound to human 11β-HSD1 also have been published. The structures show that the adamantanyl group binds close to the nicotinamide of $NADP^+$, while the carbonyl of carboxamide group interacts with the residues Ser170 and Tyr183 in the catalytic site of the enzyme. The gem-dimethyl phenoxy group of each compound sits in the hydrophobic cavity towards the mouth of the binding pocket [74].

A variety of amides and sulfonamides that contain bicyclic and bridged cycloalkylamine or adamantanyl fragments (e.g. compounds **25** and **26**) have been obtained [40, 75]. Sulfonamide **25** displays an IC_{50}=44 nM. Potency of amide **26** listed in the patent [75] is not disclosed.

Lactams represent a distinct class of 11β-HSD1 inhibitors. Many examples in this class of inhibitors contain a central pyrrolidin-2-one group, which is substituted at both the 1- and 3-positions such as compounds **27** and **28** [76]. Other examples (**29** and **30**) contain a pyrrolidin-2-one or imidazolone group as a part of the tricyclic or spiro system [77].

A variety of highly potent 11β-HSD1 inhibitors contain a substituted pyridine-2-yl aminosulfonyl scaffold. Typical examples are **31** and

32. Many of these compounds contain a 4-benzonitrile substituent as a common motif [78, 79].

Diazepane-acetamide derivatives **33** represent a novel class of potent and selective small molecule 11β-HSD1 inhibitors with a great potential for optimization in terms of pharmacological applications [80, 81]. The variability of R^1, R^2 and R^3 fragments allows extensive modification of the diazepane-acetamide structure with a considerable potential for optimization of their pharmacokinetic properties, target selectivity and species specificity.

Sulfonylpiperazin derivative **34** is known as a compound HSD-016 and is considered to be a potent, selective, and efficacious 11β-HSD1 inhibitor and advanced as a clinical candidate [82].

Thus, a wide range of chemotypes are capable of effectively inhibiting 11β-HSD1, suggesting that the enzyme active site has sufficient flexibility to accommodate a range of groups. Crystallographic studies of various compounds have suggested this observation [48-54]. However, lipophilic groups predominate in the majority of examples. Naturally, this enzyme is expressed predominantly in high lipophilic cells and tissues, and its substrate is largely hydrophobic. At the same time, the prevalence of lipophilic moieties in most inhibitors implies potential problems with solubility and metabolic stability. Most inhibitors contain a central group, such as an amide, sulfonamide, lactam or heterocycle, which is able to form a hydrogen bonding interaction with the co-factor and key aminoacid residues, such as Ser170 and Tyr183, in the active site of 11β-HSD1. These groups may also improve the physicochemical characteristics of these compounds, thus enhancing their solubility.

Limitations for development of 11β-HSD1 inhibitors are: the species-specificity of many of the compounds (the most potent inhibitors of human 11β-HSD1 are difficult to assess in rodent models); the proportionate inhibition of the enzyme that is required for its therapeutic effect (the extent to which intracellular cortisol is lowered in different tissues in humans by inhibition of 11β-HSD1). The function of 11β-HSD1 in brain and testis is not fully understood, and tissue-specific inhibition of the enzyme might be needed for optimal therapeutic benefit. Moreover, glucocorticoids are powerful anti-inflammatory agents, and are important for investigating the consequences of prolonged inhibition of 11β-HSD1 in the treatment of patients with metabolic syndrome with respect to acute and chronic inflammation in order to avoid pro-inflammatory complications [50, 56, 74].

Following the description of potential reversibility of enzyme activity in mice with H6PDH deficiency, an 11β-HSD1 inhibitor in some cases might increase, rather then decrease, intracellular cortisol concentrations [83].

Another source of adverse effects related to the 11β-HSD1 inhibition is that the metabolic clearance rate of cortisol is enhanced and that there will be a compensatory activation of the HPA axis to maintain normal blood cortisol concentration. This has been confirmed in preclinical studies with novel selective 11β-HSD1 inhibitors. In rats treated with these compounds, the adrenal gland increased in weight while the circulating corticosterone concentration remained unchanged, suggesting activation of the HPA axis [84].

The selectivity of inhibitors is of supreme importance in the prevention of any side effects associated with the ligands binding non-selectively to 11β-HSD2 or even to other hydroxysteroid dehydrogenase enzymes such as 17β-HSD or 17α-hydroxylase. As it was mentioned above, the inhibition of 11β-HSD2 leads to an over-activated MR, resulting in hypokalemia (potassium deficiency) and hypernatremia (elevated sodium levels), which, in turn, would lead to hypertension. However, this problem might be easily resolved at the stage of pre-clinical trials involving novel inhibitors.

The binding of inhibitors to alternative hydroxysteroid dehydrogenase enzymes would interfere with sex steroid metabolism, e.g. 17β-HSD inhibition would affect local estrogen metabolism [85]. Due to the fact that rodents lack the 17α-hydroxylase enzyme in the adrenal [86] and are unable to synthesise C-19 steroids such as dehydroepiandrosterone, this does not cause adverse effects in rats. However, in the human adrenal 17α-hydroxylase is present, so stimulating adrenal steroidogenesis indirectly by inhibiting 11β-HSD1 is almost certain to augment adrenal androgen production and result in hirsutism in susceptible women [35].

Despite the above-mentioned potential limitation, 11β-HSD1 inhibition remains an attractive therapeutic target for treating T2DM, obesity and MS. Since 2007, some compounds have been the objects of clinical development: INCB-13739, AMG-311 (or BVT-3498) (undisclosed structures), AMG-221 (**19**), PF-915275 (**33**), and HSD-016 (**34**) [35, 40, 56, 82]. Results from a double-blind placebo-controlled Phase IIb clinical trial involving over 300 patients with T2DM showed that treatment with once-daily doses of INCB-13739 significantly improved glycemic control, as measured by HbA1c, insulin sensitivity and total-cholesterol levels [87].

Finally, if 11β-HSD1 inhibitors as novel pharmacological agents are to be developed, where is their place in modern arsenal of anti-diabetic drugs? The current oral treatment options for T2DM include biguanide metformine, sulfonylurea or thiazolidinedione derivatives, slow digestion oligosaccharides as glycosidase inhibitors and the recently introduced dipeptidyl peptidase-4 (DPP-4) inhibitors [87, 88]. From this arsenal, only metformine and thiazolidinediones are insulin sensitizers that are well accepted as agents for MS treatment. Metformine decreases hepatic glucose production and enhances muscle sensitivity to insulin [89]. Thiazolidinediones improves peripheral and hepatic insulin sensitivity. However, these drugs have numerous adverse effects (metformine causes lactoacidosis; sulfonylureas can produce hypoglycemia and weight gain; the latter, along with cardiovascular risk, is associated with thiazolidinediones [90]; DPP-4 inhibitors may interfere with the immune system, and side effects of upper respiratory tract infections also have been reported [91]). The 11β-HSD1 inhibitors' advantage over sulfonylureas and thiazolidinediones is that they are unlikely to induce weight gain. They also have a positive effect on lipid parameters and atherosclerosis markers. Current methods of T2DM and obesity treatment target each metabolic defect and cardiovascular risk factor separately. The development of a drug that could selectively reduce the GR activation has the potential to improve within a single agent many of the metabolic abnormalities associated with T2DM and obesity. The influence of single inhibitors on the MS individual components might be modest but their combined effects will amount to substantial cardioprotection. Apart from treating MS, 11β-HSD1 inhibitors also have the potential to be an effective treatment for impaired cognition [30, 31, 56, 87]. However, proving the cardioprotective and cerebral effects of these agents will require a long and expensive clinical trial program.

Conclusion. To sum up, the therapeutic challenge is to design drugs that would provide metabolic benefits without causing major side effects. Despite the potential adverse effects mentioned above, 11β-HSD1 inhibition remains an attractive therapeutic target for treating T2DM, obesity and MS, with significant potential advantages over existing treatment options. A large variety of chemical series of compounds with this activity type holds promise of clinical success in developing this class of anti-diabetic drugs.

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Розробка інгібіторів 11β-HSD1 для впливу на метаболічний синдром

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Резюме. 11β-Гідроксистероїд дегідрогеназа (11β-HSD1) — фермент, який конвертує неактивні 11-кетоглюкокортикоїди в їх активні 11β-гідроксиформи в печінці, жировій тканині та скелетних м'язах. Хронічно підвищений рівень активності цього ферменту спричиняє ожиріння, розвиток метаболічного синдрому (МС), інсулінорезистентності, цукрового діабету 2 типу (ЦД2) і кардіоваскулярних ускладнень. Гальмування 11β-HSD1 запропоновано як стратегію зниження активності глюкокортикоїдів на тканинно-специфічному рівні. Велика кількість інгібіторів 11β-HSD1 з різних рядів азотовмісних гетероциклів нині знаходиться на різних стадіях досліджень як потенційні засоби впливу на МС і ЦД2.

Ключові слова: 11β-гідроксистероїд дегідрогеназа, кортизол, метаболічний синдром, ожиріння, розробка ліків.

References

1. *Wild S., Roglic G., Green A., Sicree R., King H.* Global prevalence of diabetes: estimates for the year 2000 and projections for 2030 // Diabetes Care. — 2004. — 27. — P. 1047-1053.

2. *Bays H.E., Chapman R.H., Grandy S.* The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys // Int. J. Clin. Pract. — 2007. — 61. — P. 737-747.

3. *Day C.* Metabolic syndrome, or what you will: definitions and epidemiology // Diabetes Vasc. Dis. Res. — 2007. — 4. — P. 32-38.

4. *Felber J.P., Golay A.* Pathways from obesity to diabetes // Int. J. Obes. Relat. Metab. Disord. — 2002. — 26 (Suppl. 2). — P. 39-45.

5. *Goodpaster B.H., Krishnaswami S., Resnick H. Kelley D.E., Haggerty C., Harris T.B., Schwartz A.V., Kritchevsky S., Newman A.B.* Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women // Diabetes Care. — 2003. — 26. — P. 372-379.

6. *Stewart P.M.* Tissue-specific Cushing's syndrome uncovers a new target in treating the metabolic syndrome-11beta-hydroxysteroid dehydrogenase type 1 // Clin. Med. — 2005. — 5. — P. 142-146.

7. *Newell-Price J., Bertagna X., Grossman A.B.* Cushing's syndrome // Lancet. — 2006. — 367. — P. 1605-1617.

8. *Tomlinson J.W., Stewart P.M.* «Cushing's disease of the omentum» — fact or fiction? // J. Endocrinol. Invest. — 2004. — 27. — P. 171-174.

9. *Seckl J.R., Walker B.R.* Minireview: 11β-hydroxysteroid dehydrogenase type 1 — a tissue specific amplifier of glucocorticoid action // Endocrinology. — 2001. — 142. — P. 1371-1376.

10. *Wamil M., Seckl J.R.* Inhibition of 11β-hydroxysteroid dehydrogenase type 1 as a promising therapeutic target // Drug Discovery Today. — 2007. — 12. — P. 504-520.

11. *Fotsch C., Wang M.* Blockade of glucocorticoid excess at the tissue level: inhibitors of 11-β-hydroxysteroid dehydrogenase type 1 as a therapy for type 2 diabetes // J. Med. Chem. — 2008. — 51. — P. 4851-4857.

12. *Sapolsky R.M., Romero L.M., Munck A.U.* How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions // Endocr. Rev. — 2000. — 21. — P. 55-89.

13. *Andreano J.M., Cahill L.* Glucocorticoid release and memory consolidation in men and women // Psychol. Sci. — 2006. — 17. — P. 466-470.

14. *Rhen T., Cidllowski J.A.* Antiinflammatory action of glucocorticoids — new mechanisms for old drugs // N. Engl. J. Med. — 2005. — 353. — P. 1711-1723.

15. *Van de Kar L.D., Blair M.L.* Forebrain pathways mediating stress-induced hormone secretion // Front. Neuroendocrinol. — 1999. — 20. — P. 1-48.

16. *Cleare A.J.* The neuroendocrinology of chronic fatigue syndrome // Endocr. Rev. — 2003. — 24. — P. 236-252.

17. *Andersen C.Y.* Possible new mechanism of cortisol action in female reproductive organs: physiological implications of the free hormone hypothesis // J. Endocrinol. — 2002. — 173. — P. 211-217.

18. *Atanasov A.G., Odermatt A.* Readjusting the glucocorticoid balance: an opportunity for modulators of 11β-hydroxysteroid dehydrogenase type 1 activity? // Endocrine, Metabolic & Immune Disorders — Drug Targets. — 2007. — 7. — P. 125-140.

19. *Stewart P.M., Krozowski Z.S.* 11beta-Hydroxysteroid dehydrogenase // Vitam. Horm. — 1999. — 57. — P. 249-324.

20. *Arnold P., Tam S., Yan L., Baker M.E., Frey F.J., Odermatt A.* Glutamate-115 renders specificity of human 11beta-hydroxysteroid dehydrogenase type 2 for the cofactor NAD^+ // Mol. Cell. Endocrinol. — 2003. — 201. — P. 177-187.

21. *Jamieson P.M., Walker B.R., Chapman K.E., Andrew R., Rossiter S., Seckl J.R.* 11β-Hydroxysteroid dehydrogenase type 1 is a predominant 11β-reductase in the intact perfused rat liver // J. Endocrinol. — 2000. — 165. — P. 685-692.

22. *Hosfield D.J., Wu Y., Skene R.J., Hilgers M., Jennings A., Snell G.P., Aertgeerts K.* Conformational flexibility in crystal structures of human 11-β-hydroxysteroid dehydrogenase type 1 provide insights into glucocorticoid interconversion and enzyme regulation // J. Biol. Chem. — 2005. — 280. — P. 4639-4648.

23. *Filling C., Berndt K.D., Benach J., Knapp S., Prozorovski T., Nordling E., Ladenstein R., Jornvall H., Oppermann U.* Protein structure and folding // J. Biol. Chem. — 2002. — 277. — P. 5677-5684.

24. *Kannisto K., Pietilainen K.H., Ehrenborg E., Rissanen A., Kaprio J., Hamsten A., Yki-Jarvinen H.* Overexpression of 11β-hydroxysteroid dehydrogenase-1 in adipose tissue is associated with acquired obesity and features of insulin resistance: studies in young adult monozygotic twins // J. Clin. Endocrinol. Metab. — 2004. — 89. — P. 4414-4421.

25. *Stewart P.M., Krozowski Z.S., Gupta A., Milandford D.V., Howie A.J., Sheppard M.C., Whorwood C.B.* Hypertension in the syndrome of apparent mineralocorticoid excess due to mutation of the 11-beta-hydroxysteriod dehydrogenase type 2 gene // Lancet. — 1996. — 347. — P. 88-91.

26. *Masuzaki H., Paterson J., Shinyama H., Morton N.M., Mullins J.J., Seckl J.R., Flier J.R.* A transgenic model of visceral obesity and the metabolic syndrome // Science. — 2001. — 294. — P. 2166-2170.

27. *Livingstone D.E., Kenyon C.J., Walker B.R.* Mechanisms of dysregulation of 11β-hydroxysteroid dehydrogenase type 1 in obese Zucker rats // J. Endocrinol. — 2000. — 167. — P. 533-539.

28. *Morton N.M., Paterson J.M., Masuzaki H., Holmes M.C., Staels B., Fievet C., Walker B.R., Flier J.S., Mullins J.J.* Novel adipose tissue-mediated resistance to diet-induced visceral obesity in 11β-hydroxysteroid dehydrogenase type-1 deficient mice // Diabetes. — 2004. — 53. — P. 931-938.

29. *Morton N.M., Densmore V., Wamil M., Ramage L., Nichol K., Bunger L., Seckl J.R., Kenyon C.J.* A polygenic model of the metabolic syndrome with reduced circulating and intra-adipose glucocorticoid action // Diabetes. — 2005. — 54. — P. 3371-3378.

30. *Chapman K.E., Seckl J.R.* 11β-HSD1, inflammation, metabolic disease and age-related cognitive (dys)-function // Neurochem Res. — 2008. — 33. — P. 624-636.

31. *Swaab D.F., Bao A.M., Lucassen P.J.* The stress system in the human brain in depression and neurode-

generation // Ageing. Res. Rev. — 2005. — 4. — P. 141-194.

32. *Morris D.J., Souness G.W. Latif S.A., Hardy M.P., Brem A.S.* Effect of chenodeoxycholic acid on 11-beta-hydroxysteroid dehydrogenase in various target tissues // Metabolism. — 2004. — 53. — P. 811-816.

33. *Arampartzis S., Kadereit B., Schuster D., Balazs Z., Schweizer R.A., Frey F.J., Langer T., Odermatt A.* Comparative enzymology of 11beta-hydroxysteroid dehydrogenase type 1 from six species // J. Mol. Endocrinol. — 2005. — 35. — P. 89-101.

34. *Pavlova S.L., Uteshev B.S., Sergeev A.V.* Licorice root: possible mechanisms of antitoxicant, anti-carcinogen, and anti-tumor properties // Pharm. Chem. J. — 2003. — 37. — P. 314-317.

35. *Hughes K.A., Webster S. P., Walker B.R.* 11-Beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors in type 2 diabetes mellitus and obesity // Expert Opin. Investig. Drugs. — 2008. — 17. — P. 481-496.

36. *Walker B.R., Connacher A.A., Lindsay R.M., Webb D.J., Edwards C.R.W.* Carbenoxolone increases hepatic insulin sensitivity in man: a novel role for 11-oxosteroid reductase in enhancing glucocorticoid receptor activation // J. Clin. Endocrinol. Metab. — 1995. — 80. — P. 3155-3159.

37. *Nuotio-Antar A.M., Hachey D.L., Hasty A.H.* Carbenoxolone treatment attenuates symptoms of metabolic syndrome and atherogenesis in obese, hyperlipidemic mice // Am. J. Physiol.: Endocrinol. Metab. — 2007. — 293. — P. E1517-E1528.

38. *Livingstone D.E., Walker B.R.* Is 11beta-hydroxysteroid dehydrogenase type 1 a therapeutic target? Effects of carbenoxolone in lean and obese Zucker rats // J. Pharmacol. Exp. Ther. — 2003. — 305. — P. 167-172.

39. *Andrews R.C., Rooyackers O., Walker B.R.* Effects of the 11 beta-hydroxysteroid dehydrogenase inhibitor carbenoxolone on insulin sensitivity in men with type 2 diabetes // J. Clin. Endocrinol. Metab. — 2003. — 88. — P. 285-291.

40. *Webster S.P., Pallin T.D.* 11-β-Hydroxysteroid dehydrogenase type 1 inhibitors as therapeutic agents // Expert Opin. Ther. Patents. — 2007. — 17. — P. 1407-1422.

41. *Su X., Vicker N., Potter B.V.L.* Inhibitors of 11β-hydroxysteroid dehydrogenase type 1 // Prog. Med. Chem. — 2008. — 46. — P. 29-130.

42. *Kotelevtsev Y., Brown R.W. Fleming S., Kenyon C., Edwards C.R.W., Seckl J. R., Mullins J.J.* Hypertension in mice lacking 11β-hydroxysteroid dehydrogenase type 2 // J. Clin. Invest. — 1999. — 103. — P. 683-689.

43. *Sandeep T.C., Andrew R., Homer N.Z.M., Andrews R.C., Smith K., Welker B.R.* Increased *in vivo* regeneration of cortisol in adipose tissue in human obesity and effects of the 11-β-hydroxysteroid dehydrogenase type 1 inhibitor carbenoxolone // Diabetes. — 2005. — 54. — P. 683-689.

44. *Schweizer R.A., Atanasov A.G., Frey B.M., Odermatt A.* A rapid screening assay for inhibition 11-β-hydroxysteroid dehydrogenases (11-beta-HSD): flavanone selectively inhibits 11-beta-HSD1 reductase activity // Moll. Cell. Endocrinol. — 2003. — 212. — P. 41-49.

45. *Lee Y.S., Lorenzo B.J., Koufis T., Reidenberg M.M.* Grapefruit juice and its flavonoids inhibit 11 beta-hydroxysteroid dehydrogenase // Clin. Pharmacol. Ther. — 1996. — 59. — P. 62-71.

46. *Ying F., Su-ling H., Wei D., Song Z., Jun-hua C., Yu S., Jian-hua S., Ying L.* Emodin, a natural product, selectively inhibits 11-β-hydroxysteroid dehydrogenase type 1 and ameliorates metabolic disorder in diet-induced obese mice // British J. Pharmacol. — 2010. — 161. — P. 113-126.

47. *Atanasov A.G., Dzyakanchuk A.A., Schweizer R.A., Nashev L.G., Maurer E.M., Odermatt A.* Coffee inhibits the reactivation of glucocorticoids by 11-β-hydroxysteroid dehydrogenase type 1: a glucocorticoid connection in the anti-diabetic action of coffee? // FEBS Lett. — 2006. — 580. — P. 4081-4085.

48. *Hosfield D.J., Wu Y., Skene R.J., Hilgers M., Jennings A., Snell G.P., Aertgeerts K.* Conformational flexibility in crystal structures of human 11β-hydroxysteroid dehydrogenase type 1 provide insights into glucocorticoid interconversion and enzyme regulation // J. Biol. Chem. — 2005. — 280. — P. 4639-4648.

49. *Johansson L., Fotsch C., Bartberger M.D., Castro V.M., Chen M., Emery M., Gustafsson S., Hale C., Hickman D., Homan E., Jordan S.R., Komorowski R., Li A., McRae K., Moniz G., Matsumoto G., Orihuela C., Palm G., Veniant M., Wang M., Williams M., Zhang J.* 2-Amino -1,3-thiasol-4(5H)-ones as a potent and selective 11β-hydroxysteroid dehydrogenase type 1 inhibitors: enzyme-ligand co-crystal structure and demonstration of pharmacodynamic effects in C57BI/6 mice // J. Med. Chem. — 2008. — 51. — P. 2933-2943.

50. *Hale C., Veniant M., Wang Z. Chen M., McCormick J., Cupples R., Hickman D., Min X., Sudom A., Xu H., Matsumoto G., Fotsch C., St Jean D.J. Jr., Wang M.* Structural characterization and pharmacodynamic effects of an orally active 11β-hydroxysteroid dehydrogenase type 1 inhibitor // Chem. Biol. Drug Des. — 2008. — 71. — P. 36-44.

51. *Wang H., Ruan Z., Li J.J., Simpkins L.M., Smirk R.A., Wu S.C., Hutchins R.D., Nirschl D.S., Van Kirk K., Cooper C.B., Sutton J.C., Ma Z., Golla R., Seethala R., Salyan M.E., Nayeem A., Krystek S.R. Jr., Sheriff S., Camac D.M., Morin P.E., Carpenter B., Robl J.A., Zahler R., Gordon D.A., Hamann L.G.* Pyridine amides as potent and selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1 // Bioorg. Med. Chem. Lett. — 2008. — 18. — P. 3168-3172.

52. *Thomas M.P., Potter B.V.L.* Crystal structures of 11β-hydroxysteroid dehydrogenase type 1 and their use in drug discovery // Future Med. Chem. — 2011. — 3. — P. 367-390.

53. *Zhang J., Osslund T.D., Plant M.H., Clogston C.L., Nybo R.E., Xiong F., Delaney J.M., Jordan S.R.* Crystal structures of murine 11β-hydroxysteroid dehydrogenase type 1: an important therapeutic target for diabetes // Biochemistry. — 2005. — 44. — P. 6948-6957.

54. *Ogg D., Elleby B., Norstrom C., Stefansson K., Abrahmsén L., Oppermann U., Svensson S.* The crystal structure of guinea pig 11β-hydroxysteroid dehydrogenase type 1 provides a model for enzyme-lipid bilayer interactions // J. Biol. Chem. — 2005. — 280. — P. 3789-3784.

55. *Boyle C.D., Kowalski T.J.* 11β-Hydroxysteroid dehydrogenase type 1 inhibitors: a review of recent patents // Expert Opin. Ther. Patents. — 2009. — 19. — P. 801-825.

56. *Hale C., Wang M.* Development of 11β-HSD1 inhibitors for the treatment of type 2 diabetes // Mini-Reviews in Medicinal Chemistry. — 2008. — 8. — P. 702-710.

57. *Alberts P., Nilsson C., Selen G., Engblom L.O., Edling N.H., Norling S., Klingstrom G., Larsson C., Forsgren M., Ashkzari M., Nilsson C.E., Fiedler M., Bergqvist E., Ohman B., Bjorkstrand E., Abrahmsen L.B.* Selective inhibition of 11 beta-hydroxysteroid dehydrogenase type 1 improves hepatic insulin sensitivity in hyperglycemic mice strains // Endocrinology. — 2003. — 144. — P. 4755-4762.

58. *Olson S., Aster S. D. Brown K., Carbin L., Graham D.W., Hermanowski-Vosatka A., LeGrand C.B., Mundt S.S., Robbins M.A., Schaeffer J.M., Slossberg L.H., Szymonifka M.J., Thieringer R., Wright S.D., Balkovec J.M.* Adamantyl triazoles as selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1 // Bioorg. Med. Chem. Lett. — 2005. — 15. — P. 4359-4362.

59. *Gu X., Dragovic J., Koo G.C. Koprak S.L., LeGrand C., Mundt S.S., Shah K., Springer M.S., Tan E.Y., Thieringer R., Hermanowsk-Vosatka A., Zokian H.J., Balkovec J.M., Waddell S.T.* Discovery of 4-heteroarylbicyclo[2.2.2]octyltriazoles as potent and selective inhibitors of 11beta-HSD1: novel therapeutic agents for the treatment of metabolic syndrome // Bioorg. Med. Chem. Lett. — 2005. — 15. — P. 5266-5269

60. *Berthiaume M., Laplante M., Festuccia W.T., Cianflone K., Turcotte L.P., Joanisse D.R., Olivecrona G., Thieringer R., Deshaies Y.* 11β-HSD1 inhibition improves triglyceridemia through reduced liver VLDL secretion and partitions lipids towards oxidative tissues. // Am. J. Physiol. Endocrinol. Metab. — 2007. — 293. — P. E1045-E1052.

61. WO 2007025880 (2007)

62. WO 2007025892 (2007)

63. WO 2005116002 (2005)

64. *ST Jean D.J., Yuan C., Bercot EA. et al.* 2-(*S*)-phenethylaminothiazolones as potent, orally efficacious inhibitors of 11β-hydroxysteroid dehydrogenase type 1 // J. Med. Chem. — 2007. — 5. — P. 429-432.

65. *Flanagan M.* Metabolic milestones // Biocentury. — 2007. — 15. — P. A1-A25.

66. *Sutin L., Andersson S., Bergquist L., Castro V.M., Danielsson E., James S., Henriksson M., Johansson L., Kaiser C., Flyrén K., Williams M.* Oxazolones as potent inhibitors of 11β-hydroxysteroid dehydrogenase type 1 // Bioorg. Med. Chem. Lett. — 2007. — 17. — P. 4837-4840.

67. WO 2005108368 (2005)

68. WO 2006074330 (2006)

69. WO 2006048750 (2006)

70. WO 2006024627 (2006)

71. *Rohde J.J., Pliushchev M.A., Sorensen B.K., Wodka D., Shuai Q., Wang J., Fung S., Monzon K.M., Chiou W.J., Pan L., Deng X., Chovan L.E., Ramaiya A., Mullally M., Henry R.F., Stolarik D.F., Imade H.M., Marsh K.C., Beno D.W.A., Fey T.A., Droz B.A., Brune M.E., Camp H.S., Sham H.L., Frevert E.U., Jacobson P.B., Link J.T.* Discovery and metabolic stabilization of potent and selective 2-amino-N-(adamant-2-yl) acetamide 11beta-hydroxysteroid dehydrogenase type 1 inhibitors // J. Med. Chem. — 2007. — 50. — P. 149-164.

72. *Sorensen B., Rohde J., Wang J., Fung S., Monzon K., Chiou W.J., Pan L., Deng X., Stolarik D., Frevert E., Jacobson P., Link J.* Adamantane 11β-HSD1 inhibitors: application of an isocyanide multicomponent reaction // Bioorg. Med. Chem. Lett. — 2006. — 16. — P. 5958-5962.

73. *Yeh V.S.C., Patel J., Yong H., Kurukulasuriya R., Fung S., Monzon K., Chiou W., Wang J., Stolarik D., Imade H., Beno D., Brune M., Jacobson P., Sham H., Link J.* Synthesis and biological evaluation of heterocycle containing adamantane 11β-HSD1 inhibitors // Bioorg. Med. Chem. Lett. — 2006. — 16. — P. 5414-5419.

74. *Sorensen B., Winn M., Rohde J., Shuai Q., Wang J., Fung S., Monzon K., Chiou W.J., Stolarik D., Imade H., Pan L., Deng X., Chovan L., Longenecker K., Junge R., Qin W., Brune M., Camp H., Frevert E.U., Jacobson P.B., Link J.T.* Adamantane sulfone and sulphonamide 11β-HSD1 inhibitors // Bioorg. Med. Chem. Lett. — 2007. — 17. — P. 527-532.

75. WO 2006094633 (2006)

76. WO 2006024628 (2006)

77. WO 2006053024 (2006)

78. WO 2005060963 (2005)

79. WO 2006106423 (2006)

80. WO 2008052638 (2008)

81. *Odermatt A.* Diazepane-acetamide derivatives as selective 11β-hydroxysteroid dehydrogenase type 1 inhibitors // Expert Opin. Ther. Patents. — 2009. — 19. — P.1477-1483.

82. *Wan Z-K., Chenail E., Li H-Q., Kendall C., Wang Y., Gingras S., Xiang J., Massefski W.W., Mansour T.S., Saiah E.* Synthesis of potent and orally efficacious 11β-hydroxysteroid dehydrogenase type 1 inhibitor HSD-016 // J. Org. Chem. — 2011. — 76. — P. 7048-7055.

83. *Lavery G.G., Walker E.A., Draper N., Jeyasuria P., Marcos J., Shackleton C.H., Parker K.L., White P.C., Stewart P.M.* Hexose-6-phosphate dehydrogenase knockout mice lack 11β-hydroxysteroid dehydrogenase type 1-mediated glucocorticoid regeneration // J. Biol. Chem. — 2006. — 281. — P. 6546-6551.

84. *Berthiaume M., Laplante M., Festuccia W., Gelinas Y., Poulin S., Lalonde J., Joanisse D.R., Thieringer R., Deshaies Y.* Depot-specific modulation of rat intraabdominal adipose tissue lipid metabolism by pharmacological inhibition of 11-beta-hydroxysteroid dehydrogenase type 1 // Endocrinology. — 2007. — 148. — P. 2391-2397.

85. *Robinzon B., Michael K.K., Ripp S.L., Winters S.J., Prough R.A.* Glucocorticoids inhibit interconversion of 7-hydroxy and 7-oxo metabolites of dehydroepiandrosteron: a role for 11beta-hydroxysteroid dehydrogenases? // Arch. Biochem. Biophys. — 2003. — 412. — P. 251-258.

86. *Van Weerden W.M., Bierings H.G., Van Steenbrugge G.J., De Jong F.H., Schroder F.H.* Adrenal glands of mouse and rats do not synthesize androgens // Life. Sci. — 1992. — 50. — P. 857-861.

87. *Sena C.M., Bento C.F., Pereira P., Seica R.* Diabetes mellitus: new challenges and innovative therapies // EPMA Journal. — 2010. — 1. — P. 138-163.

88. *Lipson V.V.* Modern approaches to research of peroral diabetes mellitus drugs // Zhurnal Org. Pharm. Khim. — 2003. — 1. — C. 59-70.

89. U.K. Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood glucose control with metformin on complication in overweight patients with type 2 diabetes (UKPDS 34) // Lancet. — 1998. — 352. — P. 854-865.

90. *Yki-Jarvinen H.* Thiazolidinediones // N. Engl. J. Med. — 2004. — 351. — P. 1106-1118.

91. *Lambeir A.M., Durinx C., Scharpe S., De Meester I.* Dipeptidyl-peptidase IV from bench to bedside: an update on structural properties, functions, and clinical aspects of the enzyme DPP IV // Crit. Rev. Clin. Lab. Sci. — 2003. — 40. — P. 209-294.